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Perturbation of Neonatal Microbial Gut Community by Peripartum Antibiotics in Wistar Rats Leads to Decreased Weight Gain

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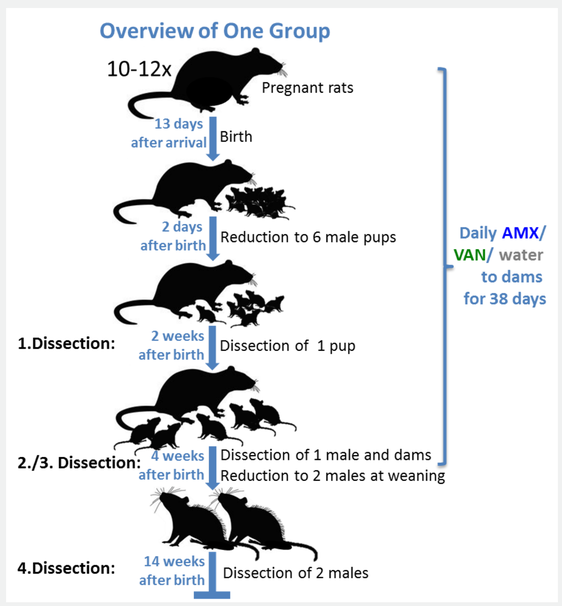
Introduction

Antibiotics are frequently administered orally to either mothers or young children to treat or prevent bacterial infections not necessarily related to the gastrointestinal system. This has adverse effects on the commensal gut microbial community, as it disrupts the intricate balance between specific bacterial groups within this ecosystem, potentially leading to dysbiosis.

We hypothesize that modulation of community composition and function induced by peripartum antibiotics affects intestinal microbial composition and general health of the offspring.



Methods

Pregnant Wistar rats (n=33) were dosed by oral gavage with either ■ amoxicillin (AMX), ▲ vancomycin (VAN), or ● water (CON) daily from 8 days before delivery until weaning of the offspring. Offspring weight-gain was recorded during the entire study period and dissections were performed at four time points (2 days, 2 weeks, 4 weeks and 14 weeks). Bacterial abundance was determined by plating of fresh fecal samples from dams right before birth. Bile acids levels were determined in the blood serum by UPLC-MS.

Results

1. Bacterial load in antibiotic treated dams, shortly before giving birth, is significantly higher than in control animals.

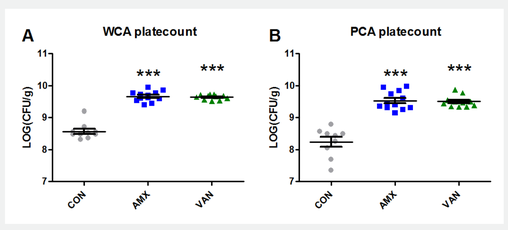


Figure 1: Bacterial abundance in feces of dams shortly before birth of offspring. (A) Abundance of anaerobic bacteria (Wilkins–Chalgren agar) and (B) aerobic Bacteria (Plate-count agar). Each dot represents an individual animal. Horizontal lines and error bars show means and SEM, respectively. Significant differences from CON group are indicated by asterisks (***; P < 0.001).

2. Significant differences in spleen, cecum, cecum pH and epididymal fat between Groups.

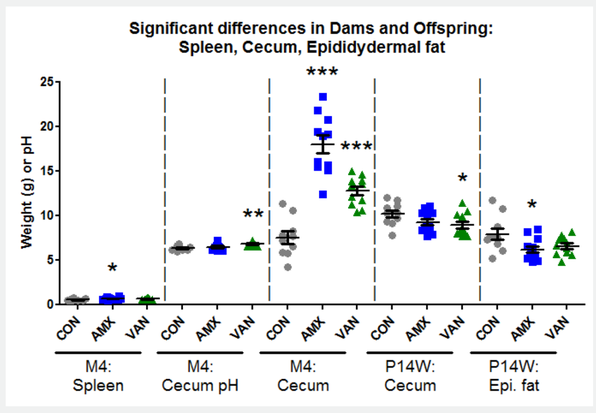


Figure 2: Significant changes in body composition. Spleen weight of dams, Cecum pH of dams, and Cecum weight of dams as well as Cecum weight of 14 week old offspring and Epididymal fat weight of 14 week old offspring. Each point represents an individual animal. Horizontal lines and error bars show means and SEM, respectively. Significant differences from CON group are indicated by asterisks (*; P < 0.05, **; P < 0.01, (***; P < 0.001).

3. Significantly lower weight gain and food intake was observed in offspring from antibiotic treated dams compared to controls.

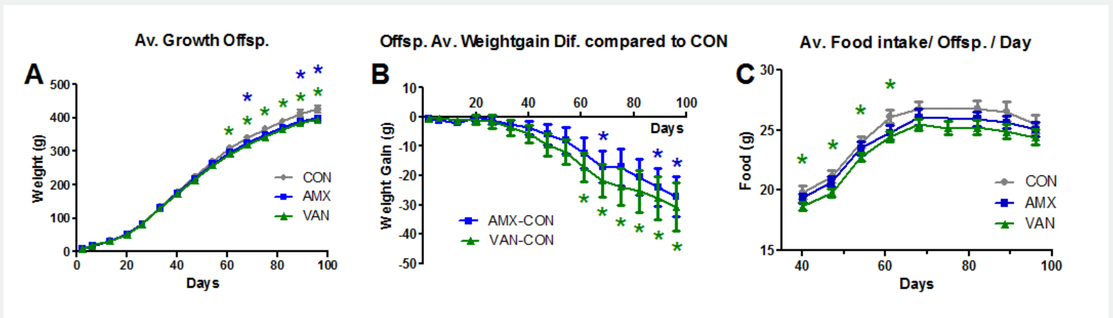


Figure 3. Weight gain and food intake in offspring. (A) Average Growth of Offspring, (B) Average weight gain difference of offspring of antibiotic treated compared to control animals and (C) Average food intake in Offspring after weaning. Each point represents a group average. Horizontal lines and error bars show means and SEM, respectively. Significant differences from CON group are indicated by asterisks (*; P < 0.05).

4. Antibiotic treatment causes significant changes of the bile acid (BA) concentration and composition in the blood serum of dams.

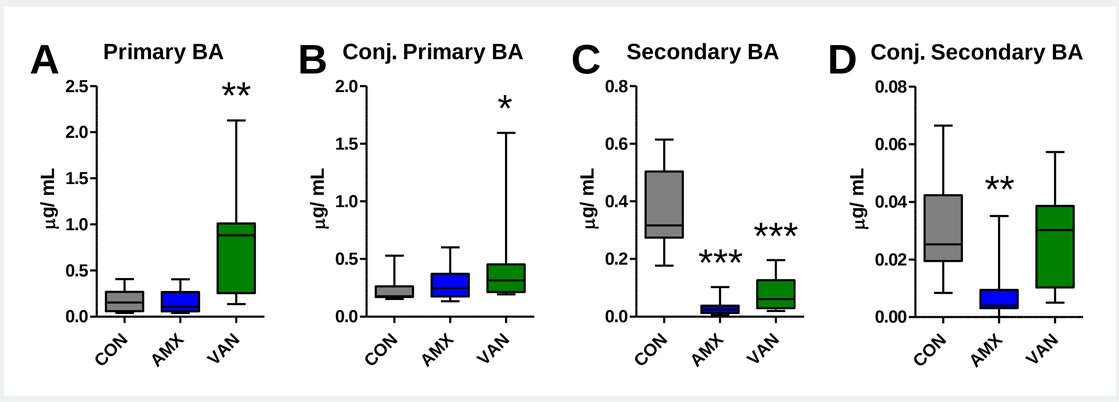


Figure 4: Sum of Primary, Conjugated Primary, Secondary and Conjugated Secondary Bile Acids. (A) Primary bile acids, (B) Conjugated primary bile acids, (C) Secondary bile acids, and (D) Conjugated secondary bile acids. Horizontal lines and error bars show means and SEM, respectively. Significant differences from CON group are indicated by asterisks (*; P < 0.05, **; P < 0.01, ***; P < 0.001).

5. Antibiotic treatment causes changes in bacterial composition.

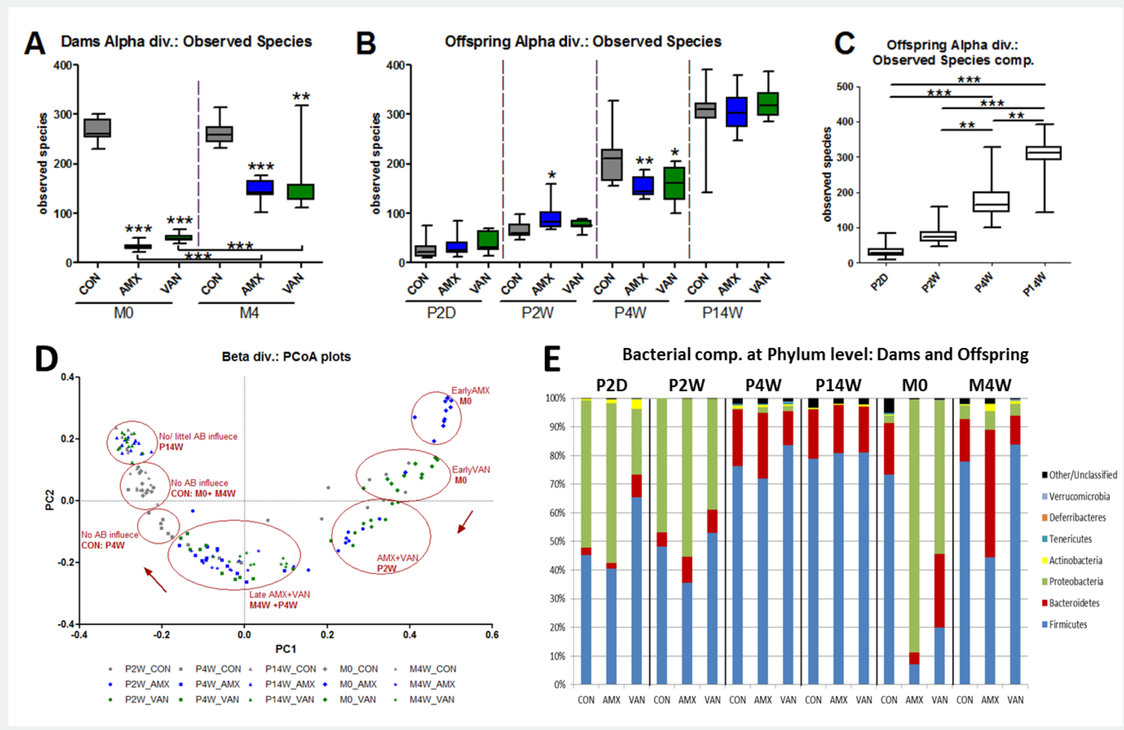


Figure 5: Changes in bacterial composition. (A) Alpha diversity Dams, (B) Alpha diversity Offspring, (C) Comparison of Alpha diversity between time points in Offspring, (D) Beta diversity of Dams and Offspring, and (E) Phylum level of Dams and Offspring. Horizontal lines and error bars show means and SEM, respectively. Significant differences from CON group are indicated by asterisks (*; P < 0.05, **; P < 0.01, ***; P < 0.001).

Conclusion

We observe reduced weight-gain in offspring of antibiotic treated dams compared to controls, even though offspring never received antibiotics directly. Additionally peripartum antibiotic treatment of rats affect cecum and epididymal fat pad weight at least 14 weeks after birth. The antibiotic treated dams show a significant increase in both aerobic and anaerobic bacteria, which constitute the inoculum for the offspring. Bile acid profiles are also changed significantly in the dams. Alpha diversity shows significant changes for both dams and offspring and beta diversity also shows a shift in bacterial composition. Changes over time are visible at phylum level for both dams and offspring, indicating a markedly different bacterial composition and activity in the gastrointestinal tract that may explain the weight difference in offspring.

Future work

GC-MS of SCFA: Analysis of short chain fatty acids in caecum

qPCR of gene expression: Examining effects of AB on satiety, tight junction proteins, Bile acid reg., immune system reg.

qPCR/ plating: Bacterial abundance in offspring

Liver fat: Analyze percentage of fat in liver

BOMB calorimeter: Analyze energy contend in feces

Elisa of gut hormones, blood lipids and inflammation factors : PYY, GLP-1, Haptoglobin, Leptin

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